Attorney Docket No.: UM-06855

REMARKS

I. Rejoinder Of Groups II & III

The Applicants gratefully acknowledge that the Examiner has rejoined Groups II & III in the present Office Action and confirm that Claims 1-18 and 21 are now pending for examination. Consequently, the Applicants have modified the status identifiers of the affected claims from "Withdrawn" to "Original". Further, the Applicants have reamended Claims 8, 9 and 13 as dependent from Claim 7 as recited in the original claim set.

II. Species Elections

The Examiner states that the claims now require species elections due to an alleged lack of unity of invention as a consequence of the above rejoinder of Groups II & III. Office Action pg 2. These proposed species elections can be summarized as follows:

In Claims 5 & 10, a species election is required as to a portion of SEQ ID NO: 93 from a properly constructed Markush group.

In Claim 8, a species election is required to an encoded protein from a properly constructed Markush group.

In Claim 9, a species election is required to a promoter sequence from a properly constructed Markush group.

In Claim 16, a species election is required to a host cell species from a properly constructed Markush group that also limits Claim 15.

The Examiner is reminded that PTO decisions are reviewed using the standard set forth in the *Administrative Procedure Act*, 5 U.S.C. § 706. *Dickinson v. Zurko*, 527 U.S. 150, 154 (1999). Under that statute, actions are set aside that are arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law. Moreover, factual findings are set aside that are unsupported by substantial evidence. *In re McDaniel*, 293 F.3d 1379, 1382 (Fed. Cir. 2002).

The Applicants traverse these species elections for the reasons presented below.

- Coombs J (1994) Dictionary of biotechnology, Stockton Press, New York NY²;
- Kurachi et al. (1993) "Biology of faxtor IX," Blood Coagul. Fibrinol. 4:953-974;
- Yao et al. (1991) "Characterization of a mouse factor IX cDNA and developmental regulation of the factor IX gene expression in liver," *Thromb. Haemost.* 65:52-58;
- Andrew et al. (1992) "Maturation of the hemostatic system during childhood," Blood 80:1998-2005;
- Andrew *et al.* (1987) "Development of the Human Coagulation System in the Full-Term Infant," *Blood* 70:165-172;
- Andrew *et al.* (1988) "Development of the Human Coagulation System in the Healthy Premature Infant," *Blood* 72:1651-1657;
- Sweeney and Hoernig (1993) "Age-Dependent Effect on the Level of Factor IX," *Am. J. Clin. Pathol.* 99:687-688;
- Kurachi *et al.* (1996) "Age and Sex Dependent Regulation of the Factor IX Gene in Mice," *Thromb. Haemost.* 76:965-969;
- Mari et al. (1995) "Hypercoagulability in Centenarians: The Paradox of Successful Aging," Blood 85:3144-3149;
- Conlan *et al.* (1993) "Associations of Factor VIII and von Willebrand Factor with Age, Race, Sex, and Risk Factors for Atherosclerosis, The Atherosclerosis Risk in Communities (ARIC) Study," *Thromb. Haemost.* 70:380-385;
- Balleisen et al. (1985) "Epidemiological Study on Factor VII, Factor VIII and Fibrinogen in an Industrial Population: I. Baseline Data on the Relation to Age, Gender, Body-Weight, Smoking, Alcohol, Pill-Using, and Menopause," *Thromb. Haemost.* 54:475-479;
- Rade *et al.* (1996) "Local adenoviral-mediated expression of recombinant hirudin reduces neointima formation after arterial injury," *Nat. Med.* 2:293-298;
- Woodward *et al.* (1997) "Epidemiology of coagulation factors, inhibitors and activation markers: The Third Glasgow MONICA Survey II. Relationships to cardiovascular risk factors and prevalent cardiovascular disease," *Brit. J. Haemat.* 97:785-797;
- Conlan *et al.* (1994) "Antithrombin III: Associations with Age, Race, Sex and Cardiovascular Disease Risk Factors," *Thromb. Haemost.* 72:551-556;

This reference is not included. If the Examiner requires this reference, we will seek to obtain it.

- Lowe *et al.* (1997) "Epidemiology of coagulation factors, inhibitors and activation markers: The Third Glasgow MONICA Survey I. Illustrative reference ranges by age, sex and hormone use," *Brit. J. Haemat.* 97:775-784;
- Finch in Longevity, Senescence, and the Genome, The University of Chicago Press, Chicago, 1990³;
- Kurachi *et al.* (1995) "Role of Intron I in Expression of the Human Factor IX Gene," *J. Biol. Chem.* 270:5276-5281;
- Ross (1995) "mRNA Stability in Mammalian Cells," *Microbiol. Rev.* 59:423-450;
- Martin *et al.* (1988) "Activation of the polyomavirus enhancer by a murine activator protein 1 (AP1) homolog and two contiguous proteins," *Proc. Natl. Acad. Sci. USA* 85:5839-5843;
- Xin *et al.* (1992) "Molecular cloning and characterization of PEA3, a new member of the *Ets* oncogene family that is differentially expressed in mouse embryonic cells," *Genes & Develop.* 6:481-496;
- Chotteau-Lelièvre *et al.*(1997) "Differential expression patterns of the PEA3 group transcription factors through murine embryonic development," *Oncogene* 15:937-952;
- Gutman and Wasylyk (1990) "The collagenase gene promoter contains a TPA and oncogene-responsive unit encompassing the PEA3 and AP-1 binding sites," *EMBO J.* 9:2241-2246;
- Yang et al. (1998) "Apolipoprotein(a) Gene Enhancer Resides within a LINE Element," J. Biol. Chem. 273:891-897;
- Caruthers et al. (1980) "New chemical methods for synthesizing polynucleotides,"
 Nuc. Acids Res. Symp. Ser. 215-223;
- Horn *et al.* (1980) "Synthesis of oligonucleotides on cellulose. Part II: design and synthetic strategy to the synthesis of 22 oligodeoxynucleotides coding for Gastric Inhibitory Polypeptide (GIP)¹," *Nuc. Acids Res. Symp. Ser.* 225-232;
- Miao et al., (1996) "Transcriptional regulation of the gene coding for human protein c," J. Biol. Chem. 16:9587-9594;
- Dieffenbach CW and GS Dveksler (1995) PCR Primer, a Laboratory Manual,
 Cold Spring Harbor Press, Plainview NY⁴;

This reference was cited in the application as a general text book without any direction to the page(s) and therefore no excerpts are included in the PTO 1449.

This reference was cited in the application as a general text book without any direction to the page(s) and therefore no excerpts are included in the PTO 1449.

- Kistner *et al.* (1996) "Doxycycline-mediated quantitative and tissue-specific control of gene expression in transgenic mice," *Proc. Natl. Acad. Sci. USA* 93:10933-10938;
- Bartlett et al. (1996) "Efficient expression of protein coding genes from the murine U1 small nuclear RNA promoters," Proc. Natl. Acad. Sci. USA 93:8852-8857;
- Sambrook *et al.* (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview NY⁵;
- Ausubel *et al.* (1989) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY⁶;
- Wigler *et al.* (1977) "Transfer of Purified Herpes Virus Thymidine Kinase Gene to Cultured Mouse Cells," *Cell* 11:223-232;
- Lowy *et al.* (1980) "Isolation of Transforming DNA: Cloning the Hamster aprt Gene," *Cell* 22:817-823;
- Wigler *et al.* (1980) "Transformation of mammalian cells with an amplifiable dominant-acting gene," *Proc. Natl. Acad. Sci.USA* 77:3567-3570;
- Colbere-Garapin et al. (1981) "A New Dominant Hybrid Selective Marker for Higher Eukaryotic Cells," J. Mol. Biol. 150:1-14;
- Hartman and Mulligan (1988) "Two dominant-acting selectable markers for gene transfer studies in mammalian cells," *Proc. Natl. Acad. Sci. USA* 85:8047-8051;
- Rhodes *et al.* (1995) "Transformation of Maize by Electroporation of Embryos," *Methods in Mol. Biol.* 55:121-131;
- Gall and Pardue (1981) "Nucleic Acid Hybridization in Cytological Preparations," *Meth. Enzymol.* 21:470-480;
- Angerer et al. (1985) "In Situ Hybridization to Cellular RNAs," in Genetic Engineering: Principles and Methods, Vol. 7 pp. 43-65, Setlow & Hollaender (Eds.) Plenum Press, NY;
- Innis *et al.* (Eds.), PCR Protocols: A Guide to Methods and Applications, Academic Press, San Diego (1990)⁷;

This reference was cited in the application as a general text book without any direction to the page(s) and therefore no excerpts are included in the PTO 1449.

This reference was cited in the application as a general text book without any direction to the page(s) and therefore no excerpts are included in the PTO 1449.

This reference was cited in the application as a general text book without any direction to the page(s) and therefore no excerpts are included in the PTO 1449.

- Hampton R. et al. (1990), Serlogical Methods a Laboratory Manual, APS Press,
 St. Paul MN⁸;
- Maddox et al. (1983) "Elevated Serum Levels in Human Pregnancy of a Molecule Immunochemically Similar to Eosinophil Granule Major Basic Protein," J. Exp. Med. 158:1211-1226;
- Hogan et al. (1986) Manipulation of the Mouse Embryo: A Laboratory Manual,
 Cold Spring Harbor, New York: Cold Spring Harbor Lab.⁹;
- Hogan et al. (1994) in Manipulating the Mouse Embryo: A Laboratory Manual,
 Cold SpringHarbor, New York, 2nd Edition¹⁰;
- Hammer et al. (1986) "Genetic Engineering of Mammalian Embryos," J. Animal Sci. 63:269-278;
- Hammer *et al.* (1985) "Production of transgenic rabbits, sheep and pigs by microinjection," *Nature* 315:680-683;
- Jaenisch (1976) "Germ line integration and Mendelian transmission of the exogenous Moloney leukemia virus," Proc. Natl. Acad. Sci USA 73:1260-1264;
- Jahner *et al.* (1985) "Insertion of the bacterial *gpt* gene into the germ line of mice by retroviral infection," *Proc. Natl. Acad. Sci. USA* 82:6927-6931;
- Van der Putten *et al.* (1985) "Efficient insertion of genes into the mouse germ line via retroviral vectors," *Proc. Natl. Acad Sci USA* 82:6148-6152;
- Stewart *et al.* (1987) "Expression of retroviral vectors in transgenic mice obtained by embryo infection," *EMBO* 6:383-388;
- Jahner *et al.* (1982) "*De novo* methylation and expression of retroviral genomes during mouse embryogenesis," *Nature* 298:623-628;
- Doetschman *et al.* (1988) "Establishment of Hamster Blastocyst-Derived Embryonic Stem (ES) Cells," *Dev. Biol.* 127:224-227;
- Tokunaga *et al.* (1989) "Establishment of the Mouse Embryonic Stem Cell Lines from Whole Blastocysts and Isolated Inner Cell Masses," *Jpn. J. Anim. Reprod.* 35:173-178;
- Eistetter (1989) "Pluipotent Embryonal Stem Cell Lines Can Be Established from Disaggregated Mouse Morulae," *Dev. Gro. Differ.* 31:275-282;

This reference was cited in the application as a general text book without any direction to the page(s) and therefore no excerpts are included in the PTO 1449.

This reference was cited in the application as a general text book without any direction to the page(s) and therefore no excerpts are included in the PTO 1449.

This reference was cited in the application as a general text book without any direction to the page(s) and therefore no excerpts are included in the PTO 1449.

- Matsui et al. (1992) "Derivation of Pluripotential Embryonic Stem Cells from Murine Primordial Germ Cells in Culture," Cell 70:841-847;
- Johnson *et al.* (1989) "Genetic Correction of Hereditary Disease," *Fetal Ther.* 4 (Suppl. 1):28-39;
- Bradley *et al.* (1984) "Formation of germ-line chimaeras from embryo-derived teratocarcinoma cell lines," *Nature* 309:255-256;
- Bradley (1987) "Production and analysis of chimaeric mice," in *Teratocarcinomas* and *Embryonic Stem Cells: A Practical Approach*," E. J. Robertson, ed., IRL Press, Oxford, UK, pp. 113-151;
- Nagy *et al.* (1990) "Embryonic stem cells alone are able to support fetal development in the mouse," *Development* 110:815-821;
- Becker et al. (1994) In Protein Expression in Animal Cells, Roth et al. eds; 11
- Davidson *et al.* (1993) "A model system for *in vivo* gene transfer into the central nervous system using an adenoviral vector," *Nature Genet.* 3:219-223;
- Shaked *et al.* (1994) "Adenovirus-Mediated Gene Transfer in the Transplant Setting," *Transplantation* 57:1508-1511;
- Graham and Prevec (1991) "Manipulation of Adenovirus Vectors," in Methods in Molecular Biology, Vol 7: Gene Transfer and Expression Protocols, pp. 109-128, Murray (ed.), Humana Press, Clifton, NJ;
- Engelhardt *et al.* (1994) "Ablation of *E2A* in recombinant adenoviruses improves transgene persistence and decreases inflammatory response in mouse liver," *Proc. Natl. Acad. Sci. USA* 91:6196-6200;
- Ledley (1995) "Nonviral Gene Therapy: The Promise of Genes as Pharmaceutical Products," *Human Gene Ther.* 6:1129-1139;
- Caplen *et al.* (1994) "Gene therapy for cystic fibrosis in humans by liposome-mediated DNA transfer: the production of resources and the regulatory process," *Gene Ther.* 1:139-147;
- Alton *et al.* (1993) "Non-invasive liposome-mediated gene delivery can correct the ion transport defect in cystic fibrosis mutant mice," *Nature Genet.* 5:135-142;
- Nabel *et al.* (1993) "Direct gene transfer with DNA-liposome complexes in melanoma: Expression, biologic activity, and lack of toxicity in humans," *Proc. Natl. Acad. Sci. USA* 90:11307-11311;
- Sanford *et al.* (1993) "Optimizing the Biolistic Process for Different Biological Applications," *Methods Enzymol.* 217:483-509;

Applicant has been unable to obtain a copy of this reference, if the Examiner request a copy we will try to obtain one.

- Yoshitake *et al.* (1985) "Nucleotide Sequence of the Gene for Human Factor IX (Antihemophilic Factor B)," *Biochem.* 24:3736-3750;
- Kurachi et al. (1998) "Improved Transfection of HepG2 Cells Using FuGENETM 6
 Transfection Reagent," Biochemica 3:43-44;
- Salier *et al.* (1990) "Functional Characterization of the 5'-Regulatory Region of Human Factor IX Gene," *J. Biol. Chem.* 265:7062-7068;
- Yao et al. (1994) "Primary myoblast-mediated gene transfer: persistent expression of human factor IX in mice," Gene Therapy 1:99-107;
- Kurachi *et al.* (1986) "Regulatory Mechanism of Human Factor IX Gene: Protein Binding at the Leyden-Specific Region," *Biochemistry* 33:1580-1591;
- Karim *et al.* (1990) "The ETS-domain: a new DNA-binding motif that recognizes a purine-rich core DNA sequence," *Genes & Develop.* 4:1451-1453;
- Nelsen *et al.* (1993) "Regulation of Lymphoid-Specific Immunoglobulin μ Heavy Chain Gene Enhancer by ETS-Domain Proteins," *Science* 261:82-86;
- Fisher *et al.* (1991) "High-affinity DNA-protein interactions of the cellular ETS1 protein: the determination of the ETS binding motif," *Oncogene* 6:2249-2254;
- Kazazian *et al.* (1988) "Haemophilia A resulting from *de novo* insertion of L1 sequences represents a novel mechanism for mutation in man," *Nature* 332:164-166;
- Dombroski *et al.* (1993) "Two additional potential retrotransposons isolated from a human L1 subfamily that contains an active retrotransposable element," *Proc. Natl. Acad. Sci. USA* 90:6513-6517;
- Minakami et al. (1992) "Identification of an internal cis-element essential for the human L1 transcription and a nuclear factor(s) binding to the element," Nucl. Acids Res. 20:3139-3145;
- Dombroski et al. (1994) "An In Vivo Assay for the Reverse Transcriptase of Human Retrotransposon L1 in Saccharomyces cerevisiae," Mol. Cell. Biol. 14:4485-4492; and
- Türkay et al. (1999) "Production of Recombinant Human Protein C In Vitro and In Vivo by Muscle Cells," Throm. Haemost. 81:727-732.

Applicants have become aware of the following documents which may be material to the examination of the above-identified application:

• Costa *et al.* (1997) "Male Infertility Caused by Epididymal Dysfunction in Transgenic Mice Expressing a Dominant Negative Mutation of Retinoic Acid Receptor α," *Biol. Repro.* 56:985-990.

- Gandolfi (1998) "Spermatozoa, DNA binding and transgenic animals,"
 Transgenic Res. 7:147-155, Abstract.
- Kurachi et al. (1998) "Mechanisms for the puberty-onset amelioration of hemophilia B Leyden: Animal model," Blood 92 (No. 10, Supplement 1):Abstract# 751.
- Kurachi *et al.* (1998) "Molecular mechanisms of homeostasis in blood coagulation: age-associated regulation of the human Factor IX gene," *Blood* 92 (No. 10, Supplement 1):Abstract #2913.
- Kurachi & Kurachi (1995) "Regulatory mechanisms of the Factor IX gene,"
 Thrombosis and Haemostasis 73(3):333-339.
- Markkula et al. (1995) "The Follicle-Stimulating Hormone (FSH) β- and Common α-Subunits are Expressed in Mouse Testis, as Determined in Wild-Type Mice and those Transgenic for the FSH β-Subunit/Herpes Simplex Virus Thymidine Kinase Fusion Gene," Endocrinology 136:4769-4775.
- Nayernia et al. (1992) "Germ Cell-Specific Expression of a Proacrosin-CAT Fusion Gene in Transgenic Mouse Testis," Molec. Repro. Devel. 31:241-248.
- O'Brien et al. (1995) "Boar Proacrosin Expressed in Spermatids of Transgenic Mice Does Not Reach the Acrosome and Disrupts Spermatogenesis," Mol. Repro. Devel. 43:236-247.
- Perry *et al.* (1999) "Mammalian Transgenesis by Intracytoplasmic Sperm Injection," *Science* 284:1180-1183.
- Robl (1999) "New life for sperm-mediated transgenesis?" *Nature Biotech.* 17:626-637.
- Smith (1999) "Sperm cell mediated transgenesis: a review," *Anim. Biotechnol.* 10:1-13, Abstract
- Yamazaki et al. (1998) "In Vivo Gene Transfer to Mouse Spermatogenic Cells by Deoxyribonucleic Acid Injection into Seminiferous Tubules and Subsequent Electroporation," Biol. Repro. 59:1439-1444.
- Youakim *et al.* (1994) "Overexpressing Sperm Surface β 1,4-Galactosyltransferase in Transgenic Mice Affects Multiple Aspects of Sperm-Egg Interactions," *J. Cell Biol.* 126:1573-1583

The following references were cited by the Examiner in the priorty case Serial No. 09/328,925 filed on 6/09/99.

• Mullins *et al.*, (1993) "Transgenesis in Nonmurine Species" *Hypertension* 22:630-633 presents a review of the current research in efforts to produce transgenic strains of rat, rabbit, sheep, goat, pig, and cow.

- Clay et al. (1999) "Potential Use of T Cell Receptor Genes to Modify Hematopoietic Stem Cells for the Gene Therapy of Cancer" Path. Oncology Res. 5(1):3-15.
- Anderson (1998) "Human gene therapy" *Nature* 392(supp):25-30.
- Hammer *et al.* (1990) "Spontaneous Inflammatory Disease in Transgenic Rats Expressing HLA-B27 and Human β_2 m: An Animal Model of HLA-B27-Associated Human Disorders" *Cell* 63:1099-1112.
- Cameron (1997) Review, "Recent Advances in Transgenic Technology"
 Molecular Biotechnology 7:253-265.
- Kurachi *et al.* (1999) "Genetic Mechanisms of Age Regulation of Human Blood Coagulation Factor IX" *Science* 285:739-743.
- Accession No. M27249, Database Embl158/Genbank 111, 4-7-1993.
- Accession No. L77890, Database Embl158/Genbank 111, 2-18-1997.

This Information Disclosure Statement under 37 C.F.R. §§ 1.56 and 1.97 is not to be construed as a representation that a search has been made, that additional information material to the examination of this application does not exist, or that any one or more of these citations constitutes prior art.

Dated: January 22, 2007

Thomas C. Howerton Registration No. 48,650

MEDLEN & CARROLL, LLP 101 Howard Street, Suite 350 San Francisco, California 94105 617.984.0616